Transcript Details

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Assessing the Current Treatment of Atopic Dermatitis: Unmet Needs

Announcer:
Welcome to Grand Rounds Nation CME on ReachMD. This is the National Jewish Health and Prova Education segment, Assessing the Current Treatment of Atopic Dermatitis: Unmet Needs.

The faculty for this activity is Donald Leung, MD, PhD, Professor and Head of the Division of Pediatric Allergy and Immunology in the Department of Pediatrics at the National Jewish Medical Center in Denver, CO.

Dr. Leung receives consulting fees from Novartis and serves as a speaker for Medimmune, Novartis, Regeneron, and Sanofi-Aventis Pharma.

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After listening to this activity, participants should be able to:

- Discuss the pathophysiologic mechanisms of atopic dermatitis (AD)
- Provide an update on the development of new management approaches for AD

Dr. Leung:
This is Dr. Donald Leung doing a lecture on Assessing the Current Treatment of Atopic Dermatitis, Unmet Needs.

I will restrict my discussion to information from publications in peer-reviewed journals.

Atopic dermatitis is the most common chronic skin disease in the United States affecting over 10% of children. It creates severe impairment in child's quality of life scores, that is comparable to renal disease and cystic fibrosis. This is because it causes severe mental distress and impairs the sleep of many families due to chronic nighttime itching. Atopic dermatitis not only affects children but can be a lifelong disease. Nearly 50% of children have persistent eczema into adulthood.

Gene association studies have revealed that there are multiple genes that affect people with atopic dermatitis. These mutations affect skin barrier function, the adaptive immune response, innate immune response and general inflammatory responses. The most common mutation that has been found are filaggrin gene mutations. Filaggrin is a protein which is found in the upper layers of skin, and in healthy individuals plays a key role in repelling allergens as well as moisturization of the skin. In patients with atopic dermatitis who have filaggrin-deficient skin, the allergens penetrate through the skin and create systemic allergic responses, including peanut allergy and local skin inflammation leading to atopic dermatitis.

Due to the marked skin barrier defect found in atopic dermatitis, randomized clinical trials have been carried out to compare the effect of using moisturizers early in life as opposed to controls. On this slide, we observed that application of moisturizer to neonates prevent development of atopic dermatitis. As a result, the American Academy of Allergy, as well as the American Academy of Dermatology, recommends that Step 1 in the management of atopic dermatitis which involves dry skin should be treated with moisturization. Step 2 is the patient who has mild to moderate eczema. Step 3a, the patient has moderate atopic dermatitis uncontrolled by Step 2 treatment. Step 3b and 4 are patients who have severe eczema that is uncontrollable with topical therapy. Step 1 should be treated with skin

hydration and barrier repair creams. Step 2 should be treated with intermittent topical steroids or calcineurin inhibitors. Step 3 should be treated with medium strength topical calcineurin inhibitors or calcineurin inhibitors on alternate days as proactive therapy. Step 3b requires more potent steroids, Step 4 systemic treatment.

This slide shows the antiinflammatory treatment options in atopic dermatitis. Topical steroids are most commonly used as a topical antiinflammatory agent since there are 7 different potencies ranging from low-potency to high-potency steroids and, therefore, give maximum flexibility. However, calcineurin inhibitors are available such as Elidel cream, which works on mild-to-moderate eczema. Protopic ointment can be used for moderate to severe atopic dermatitis. In patients who have severe, chronic, atopic dermatitis, systemic immunosuppression is often needed, and this includes oral steroids, narrow band UV light therapy, cyclosporine or other systemic immunosuppressive. It is noteworthy that, although oral steroids are commonly used by primary care physicians, they are not recommended by most subspecialists in dermatology or allergy because these patients often have severe rebound off the oral steroids.

There are certain clinical situations that favor use of topical calcineurin inhibitors over the use of topical corticosteroids. This includes patients who do not respond optimally to corticosteroid treatment, patients with face and neck dermatitis where potent topical steroid usage is undesirable, or patients who have concerns over steroid side effects such as growth, adrenal suppression or local skin atrophy and would prefer a nonsteroid approach.

This slide depicts the importance of doing proactive topical antiinflammatory therapy. In this case, patients were randomized to fluticasone cream twice a week compared to an emollient. This is a Kaplan Meier curve capturing the probability of not having a relapse in atopic dermatitis. The red line reveals that in patients using fluticasone cream twice a week, that those patients are less likely to have a relapse of their eczema. The same approach can be used in topical calcineurin-treated patients on alternate day basis.
In patients who do not respond well to topical medications, it is important to evaluate whether or not the patient fulfills key diagnostic features of atopic dermatitis. These central features include intense pruritus, chronic eczema with typical age-related skin distribution, which would include facial, neck and extensor involvement in infants and children, flexural lesions in any age group sparing of the groin and axilla. Important features seen in most cases are early age of onset, associated allergic features including an elevated IgE level and diffuse dryness.

It is important to note that a subset of patients with atopic dermatitis are prone to skin infection. This includes staph aureus or streptococcal infections, folliculitis, or a number of different viral skin infections including eczema herpeticum, molluscum contagiosum or viral warts. In patients who have infections that do not resolve quickly with therapy or are prone to recurrence, immunodeficiency should be considered, particularly in young children. However, there are a number of other conditions that can mimic atopic dermatitis. This includes contact dermatitis, metabolic disorders. In the older patient, particularly those over age 40, skin biopsies should be considered to rule out cutaneous T-cell lymphoma. And patients who have chronic infection may also masquerade as atopic dermatitis.

Other considerations in the evaluation of severe atopic dermatitis include psychosocial factors. These patients may be very depressed and therefore not be able to do routine skin care. They may be prescribed inadequate amounts of medications, or they may have certain beliefs about adverse events from medications, particularly steroid phobia, they may refuse to take baths to hydrate their skin, and cost of medications should be considered.

In managing atopic dermatitis, we should also consider whether or not the patient is exposed to triggers of atopic dermatitis. This may include irritants, foods; in the case of young children, inhalant allergens such as dust mite, animals or mold; microbial infection or contact allergens. In patients with severe eczema, it is possible for patients to present even with corticosteroid allergy.

Aside from skin barrier, we should consider the potential role that the immune response plays in driving atopic dermatitis. The strongest evidence that eczema is not only a skin barrier defect but also a skin disease that is driven by excessive immune responses is the observation that most patients with severe eczema improve with treatment with oral cyclosporine A, which targets primarily T-cell responses. There has been extensive evaluation of the immune response in atopic dermatitis. Two major T-cell pathways are the Th2 response, which starts with either the release of TSLPR interleukin 33 from epidermal cells to cause the differentiation of T-cells that produce IL-4 and IL-13. There's also increasing evidence that IL-23 may drive the differentiation of Th22 cells that produce IL-22 and alter the differentiation of keratinocytes in the skin.

Evidence for the importance of Th2 responses is shown from this paper in a recent article in JACI that evaluates skin tapes for filaggrin as well as a number of other molecules in the skin including TSLP, and what was found in this study is that the highest odds ratio for developing atopic dermatitis was a strong family history of allergies, as well as family history of allergy in combination with a high TSLP level. As you will recall from the last slide, TSLP plays a key role in driving IL-4 and IL-13. The importance of TSLP is shown on this slide where overexpression of TSLP in mice skin leads to atopic dermatitis-like lesions.

Type 2 cytokine effects have now been shown to play a critical role in driving epidermal changes in atopic dermatitis. This includes

inhibiting terminal differentiation of keratinocytes leading to low levels of filaggrin that are equivalent to levels seen in filaggrin mutations that are heterozygote, low levels of interleukin, loricrin, claudin, and corneodesmosin, which are other key epidermal proteins that are needed for skin barrier. Th2 cytokines also inhibit lipid production, antimicrobial peptides needed to fight infection, and they promote bacterial binding and colonization. All these factors link Th2 cytokines to the barrier and immune defects in atopic dermatitis.

Indeed, overexpressing interleukin 4, interleukin 13 in mouse skin leads to spontaneous development of atopic dermatitis. In humans we now are seeing evolving evidence that cytokine inhibitors such as dupilumab, which blocks signaling of the IL-4 and IL-13 receptor, led to significant improvement in clinical features of atopic dermatitis shown on this left panel using EASI, E-A-S-I, as a parameter of skin severity from eczema. Dupilumab treatment led to significant improvement in eczema compared to placebo. Itching or pruritus, as shown here on the right panel, was significantly decreased in dupilumab-treated patients compared to placebo.

The key messages from my lecture is that in a significant number of patients, atopic dermatitis persists into adulthood and significantly impacts patient and family quality of life. Atopic dermatitis is associated with a number of different atopic comorbidities including peanut allergy and asthma. Recent studies have identified a number of other nonatopic comorbidities including systemic heart disease, autoimmunity and cancer. Prevention of atopic dermatitis has been found through skin barrier protection and proactive anti-inflammatory therapy. There have been remarkable advances recently in the identification of polarized immune pathways driving atopic dermatitis. This will lead to new treatments that target polarized immune pathways such as interleukin 4, interleukin 13, IL-22, IL-17, IL-23 and different subsets of atopic dermatitis. Thank you.

Announcer:
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